Towards better surveillance of bacterial antibiotic resistance

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Mark E. Jones

MRL Pharmaceutical Services, Den Brielstraat 11, 3554 XD, Utrecht, The Netherlands

Tel: +31 30 265 1794 Fax: +31 30 265 1784
E-mail: mjones@thetsn.com

The golden age of antibiotics in the 1940s and 1950s led many scientists to the belief that infectious disease as a cause of patient morbidity and mortality was soon to become a thing of the past. Today we have a somewhat more dispassionate opinion, as dealing with the problems of antibiotic drug resistance has become an everyday task within the hospital. In many commonly encountered bacterial species, such as *Staphylococcus aureus, Streptococcus pneumoniae* and several of the Enterobacteriaceae, once uniformly susceptible to most classes of antibiotics used against them, resistance is commonplace. There have been instances where isolates have proved refractory to every potentially active compound in the pharmacy, essentially resulting in untreatable infections, a scenario reminiscent of the pre-antibiotic era. While these are extreme, rare examples, in almost every bacterial species acquired or emerging resistance to one or several drugs has been reported somewhere in the world [1,2]. From both scientific and public-health perspectives, it is imperative that we maintain an awareness of emerging bacterial drug resistance. Both the government and scientific community should be united in appreciating the need for methods in global surveillance of antimicrobial resistance to achieve this [3,4]. While consensus opinion on these factors is the first easy step, more problematic is how to implement and achieve an appropriate surveillance system that fulfills the needs of scientists, healthcare workers and public-health organizations. The ideal system should make possible the long-term surveillance and tracking of antibiotic resistance trends, be able to alert healthcare professionals to novel resistance profiles rapidly and on a daily basis, identify emerging resistance patterns, and enable scientists and prescribing clinicians alike to access the database at any time for comprehensive review and analysis. Such a system would provide resistance data which, when linked with supportive research programs in infection control and pharmaceutical usage, would allow for the development of practical measures designed to limit and ultimately reduce the burden of antibiotic resistance, at both local and national levels. To accomplish these objectives, the surveillance system would be prospective, comprehensive, responsive and necessarily automated and computerized. With the appropriate investment, today's advances in computer technology and communications make this possible.

A resistance surveillance effort is, in effect, gathering together susceptibility data and relevant clinical data, in order to create databases for subsequent analysis. To date, most surveyed susceptibility data within Europe have been derived from targeted 'point-in-time' projects focused on a particular subset of organisms or class of antibiotics, or via some of the larger surveillance studies deriving data from centralized or decentralized in vitro studies where organisms are gathered and retested using predefined panels of study antibiotics (e.g. the Alexander Project, SENTRY). The pharmaceutical manufacturing industry has played a crucial role in sponsoring many of these studies. For practical purposes, such labor-intensive studies have generally focused on particular sites of infection or subsets of organisms, or included a defined range of target drugs, which often includes investigational proprietary comparator antibiotics. Together, these have provided a wealth of susceptibility data, often standardized methodologically, which in Europe has been otherwise largely unobtainable. However, it is fair to say that across Europe such surveillance studies provide a somewhat limited 'early-warning system' and a poor ability to respond to what may be emerging trends in resistance. For example, recent work by Tenover et al. has suggested that the subset of methicillin-resistant

Staphylococcus aureus and other staphylcoccal species with an MIC of 4 mg/L for vancomycin are those most likely to go on to undergo further incremental decreases in susceptibility to this drug [5]. However, in Europe we do not have a system that enables us to respond to this information and ascertain the population and epidemiology of such phenotypes, despite the fact that thousands of staphylococci are identified and susceptibility tested to vancomycin in our laboratories daily.

An appropriate surveillance network must encompass a broad coverage of clinical microbiological institutes in the proposed region of study. If not all-encompassing (bearing in mind there are several thousand such laboratories in Europe), the system should at least be representative of all types and sizes of institution. If not, the surveillance system may not be sensitive enough to detect new emerging resistance phenotypes or detect organisms with resistance profiles of public-health concern such as vancomycin-refractory *Staphylococcus aureus*, which appear to be rare isolated events and not yet reported in Europe [6]. Including many centers in a database also allows for a better understanding of the idiosyncratic epidemiology of certain resistant phenotypes which may be of public-health importance [7] and an analysis of the database by region, often bringing to attention distinct local trends of resistance [8]. Appropriate resistance surveillance ultimately needs to be international in its scope. We can no longer be complacent about what is happening in areas other than our own. Somebody else's problem is our problem: witness the wide dissemination of penicillin-refractory *Streptococcus pneumoniae* [9,10] and methicillin-resistant *Staphylococcus aureus* [11] across Europe and beyond in a relatively short space of time. Today in Europe, political unification has erased the international frontiers between several countries; frontiers which microbes did not recognize anyway. Several studies have demonstrated the dangers of having a neighbor with a resistance problem, because of the migration of resistant clones across international frontiers [12,13].

In order to allow for the implementation of a surveillance system that can be all-encompassing in terms of geographic coverage, demographic coverage, antibiotics and organisms tested, and to have an automated system that is designed and permanently integrated as part of the normal routine day-to-day life of our hospitals, we should turn to the clinical laboratory itself. This philosophy is simple. Clinical laboratories all over Europe isolate, speciate and do susceptibility tests on organisms of clinical significance on a daily basis. Data derived from these tests are mostly stored in some form of computerized laboratory information system (LIS), and these microbiological data are used to assist in therapeutic choice in patient management within that institution. Collectively, such databases within clinical laboratories could provide a rich, comprehensive source of data, ideal for the reliable and rapid detection and surveillance of antimicrobial resistance. Today's advances in technology, particularly the Internet, allow for the collection and utilization of these data direct from the clinical laboratory information system itself for use in a surveillance system. Bear in mind that these are the very same data reported locally to clinicians and used in the management of patients and the design of local formularies. This approach to surveillance is taken by The Surveillance Network™ (TSN) and WHONet Program. The LIS data source contains all relevant clinical and microbiological information necessary for subsequent data-mining, and the capacity to provide a permanent infrastructure potentially providing surveillance of all microbiological data entered into the laboratory database. Information from all organisms and drugs tested can be collected on a daily 'real-time' basis, generally with no additional effort for the microbiology laboratory workers themselves. With this approach, laboratories, and the clinical microbiologists managing them, are returned to the front line for detection of resistance phenotypes and trends in susceptibility. In this capacity, their responsibility as an integral and necessary part of our public-health infrastructure is emphasized and nurtured. There have been some concerns about the collection of non-standardized data. A number of factors can assist in overcoming this. First, only laboratories that demonstrate microbiological proficiency and good laboratory practice in their routine daily work should be included. Accreditation, and internal and external quality control, can help with this selection. Second, ensuring that the database is appropriately balanced with respect to the susceptibility testing methodologies used allows for analysis of the database by method and thus comparison of methods. And finally, there must be a rigid enforcement of a quality control program that includes 'expert rules' that screen all data as they enter the database, for microbiological sense, internal quality control strain data, the use of appropriate methodology and correct interpretation of breakpoints. The rigid implementation of these rules is perhaps the key to the validity of such a database, as only data that pass the screening process or can be substantiated by the referring center are permitted to enter the final database used for analysis.

The raison d'être of any surveillance effort should be the utilization of data to assist us in our efforts to counteract the problems of increasing bacterial drug resistance. For this reason, optimizing access to the

susceptibility database is of paramount importance. An appropriately designed database is complex and will rapidly amass a large amount of data. In order to allow analyses of the database, the parameters to be chosen will depend entirely on the question asked, which should be able to reflect the idiosyncratic interests of individual scientists and not be restricted by the guardian(s) of the database. We must remember that the prescribing clinician is the ultimate target for our surveillance attempts, and their access to this data should not be limited to that small proportion of the potential information that is presented at scientific meetings or appears in the peer-reviewed press, so often the usual fate of surveillance-derived susceptibility data. Thus access and query-capability should be given to at least all those who provide data in the first place. In this light, the communication power provided by the Internet can be harnessed to expose surveillance data to a potentially vast audience, for on-line observation and analysis. This same communication gateway can be used to both collect and give back information in a timespan of days rather than months or even years. Such technology would provide a formidable capability for the rapid detection of emerging resistance or novel resistant phenotypes of public-health concern, and a tremendously powerful educational tool available to technical workers and heads of departments alike, so crucial in our attempts to counteract the resistance problem. The potential for heightened awareness of antibiotic resistance both locally, nationally, and internationally enables the clinical microbiologist to be aware of what susceptibility profiles to expect in their own institute, what not to expect, and what to be on the lookout for, skills that can be improved through use of the surveillance database itself. In addition, tapping directly into the clinical microbiology laboratories and working closely with the grass-roots microbiologists themselves will in turn help to stimulate the use of more reliable and appropriate protocols for resistance detection and provide a tremendous stimulus and tool for encouraging the use and development of more standardized methodologies.

It is necessary that we have comprehensive international resistance surveillance networks that are designed and dedicated to assist us in our understanding and awareness of antimicrobial drug resistance. In Europe, we need a truly all-encompassing surveillance initiative with an appropriate geographic coverage and a permanent infrastructure working alongside scientists and as an integral part of public-health infrastructure. Such a network can be achieved using the power of the Internet and the advanced information technology available today. This computer technology allows the design of an essentially automated surveillance process, enabling scientists to invest their valuable time and energy into better analysis of surveyed data, and focusing attention on those aspects of the clinical setting that also affect bacterial drug resistance, such as information concerning infection control, hospital hygiene, and antibiotic usage and consumption. Such an achievement will not be easy and is possible only if scientists, the medical community and private sector investment work hand-in-hand to reach this common goal.

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